REMARKS

Reconsideration an d withdrawal of the rejections of the application are respectfully requested in view of the remarks and amendments herein.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 1-31 are pending. Claims 1, 9, 21, 23, and 25, have been amended, without prejudice, without admission, without surrender of subject of matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that these claims, as originally presented, are in full compliance with the requirements of 35 U.S.C. 112. The new claims, as presented herein, are not added for the purpose of patentability within the meaning of 35 U.S.C. §§101, 102, 103 or 112. Rather, these claims are added for clarification and to round out the scope of protection to which Applicants are entitled.

II. CORRECTION OF INVENTORSHIP

In view of the finalized Restriction Requirement, applicants respectfully request deletion of Rikke Skjot as an inventor under 35 USC 1.48(b). The Commissioner is hereby authorized to charge the fee therefor and any additional fees occasioned by this paper, or credit any overpayment in fees, to Deposit Account 50-0320.

III. THE OBJECTIONS TO THE DRAWINGS ARE OVERCOME

The Drawings were objected to as allegedly unsuitable for publication due to various formalities. The amendments to the application herewith provide new formal drawings. Accordingly, reconsideration and withdrawal of the objection to the drawings is respectfully requested.

IV. THE COMMENTS AS TO PRIORITY OF THE APPLICATION ARE NOTED

The Office Action requests that the priority information contained on the first page of the specification be updated, and requests that a certified translation of the priority document,

PA199701277 be provided. Applicants note the requests, and respectfully submits that these will be attended to in a separate communication.

V. THE OBJECTIONS TO THE SPECIFICATION ARE OVERCOME

The specification was rejected due to a series of spelling errors and informalities. It is respectfully submitted that the amendment herein corrects such defects rendering the objection moot. Consequently, reconsideration and withdrawal of the objection to the specification is respectfully requested.

VI. THE OBJECTIONS TO THE CLAIMS ARE OVERCOME

Claims 21, 23, and 25 were objected to as allegedly being directed to nonelected species. Applicants respectfully traverse the objections. It is respectfully submitted that the amendment of claims 21, 23, and 25 renders the objection moot.

Consequently, reconsideration and withdrawal of the objections to the claims are respectfully requested.

VII. THE REJECTIONS UNDER 35 U.S.C. §101 ARE OVERCOME

Claim 9 was rejected under 35 U.S.C. §101 as allegedly being in an improper claim format. The amendments to the claims herewith serve to place the claims in proper form for U.S. prosecution, rendering the rejection moot. Consequently, reconsideration and withdrawal of the rejection is respectfully requested.

VIII. THE REJECTIONS UNDER 35 U.S.C. §112 ARE OVERCOME

Claims 1-11, 21, 23, and 25-30 were rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. The rejection is respectfully traversed.

Specifically, the use of the term "derived" was considered to render the claims indefinite. Applicants respectfully urge that amendment of claims 1 and 23 renders the rejection moot.

Additionally, the Office Action states that it is unclear what the metes and bounds are for determining sequence identity for the analogues of the fusion polypeptide having ≥70% identity. Applicants respectfully disagree.

In claim 1, the percen tage of homology is related to ESAT-6 and Ag85B, both of which are kn own polypeptides having sequences well-known to the skilled person and depicted in SEQ ID NO 1 and 2, respectively. Further, examples of fusion polypeptides are found in SEQ ID Nos 3 and 4, such that, contrary to the Office Action's assertion, sufficient disclosure is provided in the specification to render the claims definite.

Consequently, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 8, 9, 11, 25, and 27 were rejected under 35 U.S.C. §112, first paragraph. The Office Action (at 6-11, Items 18-20) asserts that the Applicants have not (1) shown possession of the claimed invention in relation to human vaccines; (2) enabled the claimed invention; or (3) shown cross-protection of the vaccine for other species of mycobacteria than M. tuberculosis. The rejections are respectfully traversed, and will be addressed collectively.

Applicants respectfully request reconsideration and withdrawal of the rejection in light of the following discussion.

The Office Action (at 7) asserts "*...historically, the failure of effective vaccines to protect humans against infection with M. tuberculosis even though the vaccines were successful in animals...is notorious for a lack of successful protection.*"

At the time of filing the present application, no new tuberculosis vaccines have been registered since the widespread acceptance of M. bovis BCG. However both *M. bovis* BCG and the Orkney vole bacterium *M. microti* have been tested in humans and both have been shown to be protective (see Hart PD and Sutherland I, 1977, Br Med J 22:293-295). The failure of *M. microti* BCG to become a registered vaccine has nothing to do with its efficacy, which was reckoned equivalent to BCG, but reflects the fact that it offered no significant advantage over BCG, a registered vaccine already in use. As noted above (and see, for example, Manabe, Infect. Immun. 2002 Mar;70(3):1566-70) both of these vaccines are effective in animals and also effective in humans. The basis, therefore, for the assertion of historical failure of *M. tuberculosis* vaccines is unclear. It is true that no recombinant vaccines have yet given proof of efficacy in humans. However, a clinical phase III trial of a tuberculosis vaccine candidate is believed to take from 10 to 15 years requiring 7,000 to 300,000 subjects. According to NIH (Blueprint for Tuberculosis Vaccine Development, 1998) it could take 20 to 30 years to evaluate protective efficacy fully. Given the state of the art 20 years ago, it is of no surprise that we have no data on recombinant vaccines today, as none have yet been tested for efficacy in humans. As noted

above, the current BCG vaccine against tuberculosis has been used in humans for over 6o years, and although it is far from perfect, BCG has amply demonstrated high levels of efficacy when given under ideal conditions. This vaccine was originally selected after screening in animal models (see for example A. Calmette "La Vaccine Preventative Contre la Tuberculose par le BCG" Pub. Masson et Cie, Paris 1927, which describes a variety of animal studies in detail). Therefore, it is clear that efficacy in humans does in fact correlate with efficacy in animal models in the two instances where a full data set is available. In contrast, Applicants are unable to find any support for the contention that vaccines demonstrating a high level of efficacy in animal models have undergone efficacy testing and failed in humans.

The Office Action (at 7) further asserts "*In addition, at the time of filing of the instant specification, there remained a lack of correlation of success in animal models with successful vaccination of humans...*"

In addition to the comments above, in the absence of any full-scale human trials of new vaccines, there is no data to evaluate apart from that generated with BCG and *M. microti*, which are examples of correlation between animal models and human vaccination. The fact that there have been no new tuberculosis vaccines tested in the recent past does not mean that there will be no new tuberculosis vaccines ever. This logic could be applied to any vaccine before it has been tested and would suggest that there could be no new vaccines of any sort. However, no one skilled in the art would suggest that vaccines should be tested in humans without any prior indication of efficacy in other animals. Significant effort has been expended by the scientists involved in tuberculosis research (those, who are by definition, skilled in the art) to optimise animal models for vaccine screening. With regard to the problem of selecting vaccine candidates for human trials, Wiegeshaus and Smith (Review of Infectious Diseases, vol 11, supplement 2, s484-s490, 1989) conclude that "*The logical solution is to adopt a rational animal model designed to stimulate the conditions under which humans are vaccinated and infected to measure a protective response based on an understanding of the pathogenesis of TB in humans.*" One such rational animal model was recently described by Brandt et al. (J. Immunol., 3527-33, 1996) and involves using IFN-gamma release from lymphocytes from vaccinated mice as a measure of vaccine immunogenicity and reduction in bacterial growth as a measure of vaccine efficacy. This model has been tested in various laboratories and is recognized worldwide as the best model for testing vaccine candidates against tuberculosis and has been used since. It is likewise agreed

that the guinea-pig is a good model to study the pathology of tuberculosis. Applicants respectfully note that Orme et al (Infectious Disease Clinics of North America, Vol. 13, No. 1, 1999) concludes that the mouse is a suitable model for TB in humans: on page 169 it is stated with regard to mouse models that "*...these models are not the real thing, but it can be strongly argued that much of the information uncovered in the mouse model...is clearly operative in human being;"* and at page 176, with respect to the guinea pig as a model, "*This is labour intensive and expensive work but necessary before a given candidate for primate testing or human clinical trials can be taken seriously.*" The proposition that animal models have no predictive value for tuberculosis vaccine development therefore directly contradicts the conclusions of experts working in the field. Moreover, this proposition is not substantiated by BCG, the only tuberculosis vaccine to have progressed through prolonged evaluation in humans to clinical deployment. In this context, it should be pointed out that factors initially identified in mouse models of tuberculosis as contributing to the pathogenesis of the disease (see, for example, the role of IFN-gamma in the control of infection described in Flynn, et al. 1993. J. Exp. Med. 178, 2249) were later confirmed in human studies (Ottenhoff, et al. 1998. Immunol. Today 19, 491) and are now the basis of clinical treatments (Holland SM. Semin Respir Infect. 2001 Mar; 16(l),47-59). Therefore, mechanisms underlying immunity to tuberculosis in mice and humans are closely related, and IFN-gamma levels are powerful predictive parameters for assessing the efficacy of immune responses in animal models and humans. Indeed, IFN-gamma therapy is now given to humans with recalcitrant mycobacterial infections.

The Office Action (at 7) notes that "*...the only examples taught in the instant specification do not involve protection of humans against infection with M. tuberculosis, but only laboratory animals, i.e. guinea pigs, mice, and monkeys, which are not hosts for normal infection with M.tb.*"

Although mice are not normal hosts for M. tuberculosis, they do contract a disease with many similarities to the human disease following exposure to M. tuberculosis (e.g., localisation of the bacteria to the lung, consolidation of the lung, granuloma formation, etc.). As pointed out above, the immune system per se appears to function similarly in humans and mice. Moreover, the BCG vaccine, which is partially effective in humans against *M. tuberculosis* is also partially effective in mice, guinea pigs and primates. Therefore, although the different species are not identical, the mice and other animal models appear to share many features, both regard to disease

and with regard to protective immunity, making them useful for studying the effect of a vaccine candidate against tuberculosis.

The Office Action (at 8) concludes "*Therefore, based on the historical lack of any effective vaccipating agent...against M.tuberculosis, and the lack in the instant application of any human data showing the instantly claimed agent being effective..., the instant application does not reasonable convey...that the inventors...had possession of the claimed invention, i.e., a vaccinating agent for promoting, in humans, an effective immune response against M.tuberculosis.*"

Applicants respectfully urge that the above conclusion is not justified in the absence of supporting data. It is agreed that mice and guinea pigs are not natural hosts on *M. tuberculosis*. However, this does not mean that immunity to *M. tuberculosis* cannot be studied in these animals, since as noted above, disease in these species shares many features in common with disease in humans, as does their response to vaccination. Whooping cough, for example, is not a natural disease of mice, but the mouse protection assay is used to assess the efficacy of vaccines for human use against Bordetella pertussis, the causative agent of whooping cough (see, for example, STATEMENT ON PERTUSSIS VACCINE - CCDR Vol.23 ACS-3 from the Canada Communicable Disease Report where it states explicitly "*For whole-cell pertussis vaccines, vaccine potency and efficacy correlate with a minimum of four international units (IUs) in the intracerebral mouse-protection assay*"). In the vaccine art, therefore, natural host range does not define the appropriateness of an animal model. The relevant parameters are rather the type of immune response generated by infection and/or vaccination and the pathology attendant on infection. It is respectfully submitted that these parameters in the chosen animal models fall within the spectrum observed for human disease.

The Office Action (at 10) asserts "*The relative skill of those in the art of production of vaccines against M. tuberculosis in experimentally infected animals is high and has been successful. However, to date, other than M. bovis BCG, the production of any other vaccine against M. tuberculosis in humans has been totally unsuccessful.*"

Applicants respectfully note that large-scale human studies conducted in the 1960s in the United Kingdom suggested that *M. microti* is also protective in humans (see Hart PD and Sutherland I, 1977, Br Med 7 22:293-295). This vaccine is also functional in animal models (see Manabe, *supra*). As of today, 3 live vaccines (*M. vaccae*, *M. bovis* BCG and *M. microti*) have

been tested in humans. All show some degree of protection against tuberculosis in humans. And all show some degree of protection in animal models. However, since these vaccines are expected to suffer from the same failings as BCG, such as sensitivity to prior immunity (see Brandt et al., Infect Immun. 2002, 70, 6728) they have not progressed to registration. It is generally acknowledged that a novel vaccine capable of mimicking BCG's efficacy in animal models and not subject to the same limitations would be of great utility. Indeed, the hybrid molecule, which is the subject matter of the present application, has been selected for an up-coming clinical Phase I trial recommended and financed by the European Union, after independent analyses by a panel of experts in the field of tuberculosis vaccine development.

The Office Action (at 10) asserts that "*The quantity of experimentation necessary to produce a vaccinating agent in humans to protect against M. tuberculosis infection constitutes at this point in time merely an invitation for experimentation without reasonable expectation of success.*"

Applicants respectfully submit that given the direct correspondence between success in the only two large scale human trials so far conducted, and protective efficacy in animal models of tuberculosis using the same vaccines, that animal testing is the only predictor of vaccine efficacy currently available. Indeed, rather than inviting "*experimentation without a reasonable expectation of success*" eliminating animal testing (which would be the only logical step if these models are not predictive) would ensure that vaccines were tested more or less at random in human populations since no criteria of efficacy other than success in animal testing exists. It is clear that regulatory authorities will not accept human studies without prior evidence of efficacy in animal models. This being the case, it is difficult to see why these efficacy studies are asserted to be irrelevant.

The Office Action (at 11) notes "*The presence or absence of working samples - the only examples taught involves protection of experimentally infected laboratory animals. The instant specification does not indicate any cross-protection using the claimed fusion protein.*"

Contrary to this statement, the inventive Hybrid1 vaccine of the present application has been shown to have protective efficacy in mice, guinea pigs and non-human primates. Therefore, the Hybrid1 vaccine shows protection both in genera which do not naturally suffer from tuberculosis as well as in non-human primates, which are not only natural hosts for tuberculosis, but also closely related to humans (see, for example, Montali et al., Rev Sci Tech

2001 Apr; 20(1):291-303). Likewise, BCG, the only vaccine shown to have efficacy in humans, is protective in these species to approximately the same level as the Hybridl vaccine (see for example, langemans et al., Proc Natl Acad Sci U S A. 2001 Sep 25;98(20):11497-502).

With respect to cross-protection, Applicants respectfully note that ESAT6 and Ag85B proteins are well-conserved within the species of the mycobacterium tuberculosis complex. Indeed, ESAT6 and Ag85B amino acid sequences are identical between *M. tuberculosis* and *M. bovis* (cf. GenBank accessions AA062005, S29663, NP_218392, and 2209337A).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections.

CONCLUSION

In view of the remarks and amendments herein, the application is now in condition for allowance. Consequently, reconsideration and withdrawal of the rejections, and prompt issuance of a notice of allowance, are respectfully requested.

Respectfully submitted,

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